

Attorney Docket No.: **MGU-0027**  
Inventors: **Hanrahan and Luo**  
Serial No.: **10/790,273**  
Filing Date: **March 1, 2004**  
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**REMARKS**

Claims 1-8 are pending in the instant application. Claims 1-6 have been withdrawn from consideration and canceled. Claims 7 and 8 have been rejected. Claim 7 has been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

**I. Election/Restriction**

The restriction requirement placing the claims into Groups I-III has been deemed proper and made final. Claims 1-6 have been withdrawn from further consideration. Accordingly, Applicants are canceling claims 1-6 without prejudice, reserving the right to file continuing applications for the canceled subject matter.

**II. Rejection of Claims Under 35 U.S.C. §112**

Claims 7-8 have been rejected under 35 U.S.C. 112, first paragraph. It is suggested that the specification, while being enabling for a method of identifying an agent that facilitates folding and exit of a normally cell surface-localized transmembrane domain-containing protein from the endoplasmic reticulum, wherein said protein is tagged with a biotin target sequence in the extracellular domain, is not enable for a method for identifying an agent which corrects misfolding of a membrane-localized protein, wherein said protein is tagged with a biotin target sequence. It is further suggested that the invention recites the identification of agents for membrane-localized proteins; however, the Examiner alleges that the invention only works for mutant forms of proteins normally localized to the plasma membrane which are retained in the

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ER by the ER quality control apparatus. Applicants respectfully disagree with this rejection.

As disclosed at page 14, lines 6-17, a membrane-localized protein of the invention can have a biotin target sequence tag incorporated into at least one extracellular or intracellular loop domain so that the upon exposure to biotin ligase and biotin, the membrane-localized protein is labeled. In this regard, the biotin ligase can be exogenously provided to the cell for extracellular loop domain labeling, or alternatively, the biotin ligase can be expressed by the cell for intracellular loop domain labeling (see the paragraph bridging pages 18 and 19). Accordingly, in an earnest effort to clarify the location of the biotin target sequence, Applicants have amended claim 7, in accordance with the disclosure at page 14, lines 6-17, to indicate that the membrane-localized protein is tagged in a loop domain with a biotin target sequence.

Applicants have appreciated that biotin tagging of a misfolded mutant membrane-localized protein can be used to identify agents which modulate trafficking of the mutant membrane-localized protein through the ER to the plasma membrane. See the passage between page 20 (line 15) and 25 (line 24). Correct protein folding and localization is detected by the presence of the biotinylated membrane-localized protein at the plasma membrane (see page 23, line 27, to page 24, line 4). Thus, to further clarify the instant method and place the claims in better form for consideration, Applicants have amended claim 7, in accordance with the disclosure at pages 20-25, to indicate that the protein being assayed is a mutant membrane-localized protein and the readout of the assay is the presence of biotin-labeled protein at the plasma membrane of the cell.

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Applicants respectfully submit that the instant disclosure contains a sufficient amount of information regarding the subject matter of the claims as amended to enable one skilled in the pertinent art to make and use the claimed invention. Thus, the enablement requirement has been met and it is respectfully requested that this rejection be reconsidered and withdrawn.

### **III. Rejection of Claims Under 35 U.S.C. §103**

Claims 7 and 8 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Schatz (U.S. Patent No. 5,874,239) and further in view of Heda et al. (2000) *Biochem. Biophys. Res. Commun.* 271:659-664). It is suggested that Schatz discloses biotin target sequences of the instant application for use in fusing generically to polypeptides for efficient biotinylation of the resulting fusion proteins. It is suggested that while Schatz teaches exposing the tagged protein to biotin and adding exogenous biotin ligase, Schatz does not disclose biotinylation of cell surface proteins in an assay to identify agents that facilitate folding of an ER-retained membrane localized protein. The Examiner suggests that Heda et al. compensate for the deficiencies in Schatz by teaching biotinylation of the cell surface and total CFTR in an assay to identify agents that correct protein misfolding of CFTR. It is suggested the Heda et al. teach obtaining a cell culture which expresses a misfolded membrane-localized protein (CFTR), and performing surface biotinylation by cross-linking biotin to all proteins containing glycosyl moieties after exposing the culture to low temperature or sodium butyrate (agents that potentially correct misfolding of CFTR), wherein an increase in labeled CFTR indicates the agent works. It is also suggested that Heda et al. teach

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contacting the cell with a permeabilizing agent before detection (page 680, left column, top paragraph). The Examiner alleges that Heda et al. instructs as to how to use surface biotinylation in an assay designed to identify agents that correct misfolded CFTR that remains stuck in the ER, wherein if the agent does not work, there is no cell surface biotinylation of CFTR. It is suggested that because Schatz discloses that a short biotin tag can be added to the target protein and will be biotinylated in the presence of biotin ligase, one of ordinary skill in the art would have been motivated to combine the biotin tag of Schatz with the surface glycosyl moiety biotinylation of Heda et al. because the tag of Schatz provides a more specific labeling of CFTR, and eliminates having to use a second, CFTR-specific antibody in the detection step. Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). In this regard, a *prima facie* case of obviousness has not been established on the basis of the Examiner's comments and the cited prior art references.

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While the Examiner suggests that "one of ordinary skill in the art would have been motivated to combine the biotin tag of Schatz with the surface glycosyl moiety biotinylation of Heda et al. because the tag of Schatz provides a more specific labeling of CFTR, and eliminates having to use a second, CFTR-specific antibody in the detection step", a general incentive does not make obvious a particular result, nor does the existence of isolated techniques by which that particular result can be obtained. See *In re Deuel*, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995). What is required is "some objective teaching in the prior art or ... knowledge generally available to one of ordinary skill in the art [that] would lead that individual to combine the relevant teachings of the references." *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). The examiner has not pointed to factual evidence in the cited references that would lead one of ordinary skill in the art to prepare a mutant membrane-localized protein with a biotin sequence tag of Schatz for use in an assay of Heda et al. Thus, the statements made by the Examiner amount to no more than conclusory statements of generalized advantages and convenient assumptions about skilled artisans. However, such statements and assumptions are inadequate to support a finding of motivation, which is a factual question that cannot be resolved on "subjective belief and unknown authority." *Lee*, 277 F.3d at 1344.

Furthermore, while Schatz discloses biotin labeling of cell membrane receptors, Schatz does not specifically disclose how to go about labeling a cell membrane receptor such that one of skill the art could achieve labeling of a cell membrane receptor with a reasonable expectation of success. In particular, Schatz does not teach or suggest specifically incorporating a biotin sequence tag

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into the loop domain of a mutant membrane-localized protein. In fact, Schatz only exemplifies biotin tagging at the N-terminus of cytoplasmic maltose binding protein. See column 12, lines 46-49, and Example 3 of Schatz. Thus, at best, Schatz teaches biotin tagging of a cytoplasmic protein, with insufficient direction to enable the preparation and use of a biotin target sequence to tag a membrane-localized protein. A conclusion of obviousness requires that the reference(s) relied upon be enabling in that it put the public in possession of the claimed invention. MPEP §2144.08.

Moreover, as presently claimed, the instant method requires that after contacting the cell with a test agent, the effect of the test agent on the mutant membrane-localized protein is determined by detecting the presence of labeled mutant membrane-localized protein in the plasma membrane of the cell. The cited references neither teach nor suggest this limitation. In particular, the assay of Heda et al. requires biotin labeling of CFTR at the cell surface and streptavidin extraction to detect labeled CFTR. See the paragraph bridging columns 1 and 2 at page 661. As such, Heda et al. do not teach or suggest detecting the presence of labeled mutant membrane-localized protein in the plasma membrane as the CFTR being detected by Heda et al. is a protein extracted from the plasma membrane. Likewise, there is no teaching or suggestion by Schatz to detect trafficking of membrane-localized proteins to the plasma membrane. The *prima facie* case must account for all the limitations of the claims. See *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1275, 23 USPQ2d 1839, 1840 (Fed. Cir. 1992) ("[E]ach claim is an entity which must be considered as a whole," emphasis in original); *In re Angstadt*, 537

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F.2d 498, 501, 190 USPQ 214, 217 (CCPA 1976) ("[W]e must give effect to all claim limitations," emphasis in original).

Lastly, the Examiner alleges that at page 660, left column, top paragraph, Heda et al. report contacting the cell with a permeabilizing agent before detection. However, Applicants find no reference to a permeabilizing agent such as those disclosed at page 24, lines 23-30, of the instant specification.

Because the Examiner has failed to provide substantial evidence for a motivation to combine the cited prior art references and the prior art references fail to enable or teach every limitation of the claimed invention, a *prima facie* case of obviousness has not been established as required under 35 U.S.C. 103(a). It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

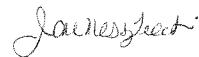
#### **IV. Conclusion**

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

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favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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